PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 47/40 — A1

(11) International Publication Number: WO 95/32737

(43) International Publication Date: 7 December 1995 (07.12.95)

(21) International Application Number: PCT/GB95/01152

(22) International Filing Date: 22 May 1995 (22.05.95)

(30) Priority Data:
94/3740 27 May 1994 (27.05.94) ZA

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(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published
With international search report.

(54) Title: PHARMACEUTICAL COMPOSITION

(57) Abstract

A method of making a pharmaceutical composition comprising an inclusion complex of a β-cyclodextrin or a derivative thereof and a sparingly water-soluble non-steroidal anti-inflammatory drug such as diclofenac sodium, the composition being in solid form which is adapted to be dissolved in water to provide a clear or slightly opaque solution for oral administration, includes the steps of forming a paste from the β-cyclodextrin or the derivative thereof and the NSAID with a wetting solution, mixing the paste with addition of further wetting solution if necessary, and drying the product to produce the inclusion complex which dissolves in water to provide a clear or slightly opaque solution.

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PHARMACEUTICAL COMPOSITION

BACKGROUND OF THE INVENTION

This invention relates to a method of making a pharmaceutical composition comprising an inclusion complex of a β-cyclodextrin, or a pharmaceutically acceptable derivative of a β-cyclodextrin and a sparingly water-soluble non-steroidal anti-inflammatory drug (NSAID), and to a pharmaceutical composition comprising an inclusion complex of a β-cyclodextrin or a derivative thereof and a sparingly water-soluble NSAID, in solid form which is adapted to be dissolved in water to provide a clear or slightly opaque solution for oral administration.

Non-steroidal anti-inflammatory drugs (NSAID's) are generally practically insoluble in water. The low solubility impedes the dissolution rate of the drug in the gastrointestinal tract, resulting in slow absorption. Consequently, for most NSAID's, peak plasma levels are usually reached only after one to several hours after oral administration, depending on the solubility of the drug. NSAID's commonly formulated as tablets therefore suffer from two disadvantages: (i) delayed onset of therapeutic action and (ii) local irritation of the gastrointestinal mucosa due to prolonged localised contact of the drug with the mucosa.

Attempts to solubilise NSAID's via salt formation have been reported, resulting in an improved absorption rate (see Reference 1). Several reports have appeared on complexation of NSAID's with cyclodextrins in which the complexes show significantly improved aqueous dissolution characteristics (see References 2, 3, 4, 5, 6, 7). Apart from enhancement of water solubility, cyclodextrin complexation has also been shown to increase the rate and extent of NSAID adsorption after oral administration (see References 2, 8). A further advantage of cyclodextrin complexation is a reduction in the ulcerogenicity commonly associated with orally administered NSAID's (see Reference 9).

Cyclodextrin inclusion complexes may be prepared on the basis of liquid state, solid state or semi-solid state reaction between the components (see Reference 10). The first is accomplished by dissolving the cyclodextrin and NSAID in a suitable solvent and subsequently isolating the solid state complex by crystallisation, evaporation, spray drying or freeze drying. In the solid state method, the two components may be optionally screened to uniform particle size and thoroughly mixed whereafter they are ground in a high energy mill with optional heating, screened and homogenized (see South African Patent No. 91/2282). In the semi-solid state, the two components are kneaded in the presence of small amounts of a suitable solvent, and the complex so-formed, is oven dried, screened and homogenized (see Reference 11).

In terms of completeness of the inclusion complexation reaction, the particle size and the water solubility of the final product, the freeze-drying and spray drying methods represent the best methods of inclusion complexation (Reference 10). These methods however are economically unattractive from

an industrial perspective. Owing to the physicochemical nature of NSAID's it was found that the industrially simple and economically attractive kneading method provided a convenient process for the preparation of NSAID-cyclodextrin complexes with the desired water solubility.

As stated above, various pharmaceutical compositions containing inclusion compounds or complexes of a cyclodextrin and a drug are known.

South African Patent No. 84/10042 to Janssen Pharmaceutica N.V. discloses a pharmaceutical composition comprising an inclusion compound of an unstable or sparingly water-soluble drug and a partially etherified β-cyclodextrin of the formula
(β - CD) OR
in which the residues are hydroxyalkyl groups and in which part of the residues R may optionally be alkyl groups, the β-cyclodextrin ether having a water-solubility of more than 1,8g in 100ml of water. The drug may be a non-steroidal anti-rheumatic agent. The partially etherified β-cyclodextrin is preferably hydroxyethyl or hydroxypropyl β-cyclodextrin.

The inclusion compound is prepared by dissolving the partially etherified β-cyclodextrin in water and adding the drug. The pharmaceutical composition may be formulated for oral administration.

PCT WO/90/02141 to Australian Commercial Research and Development Limited teaches inclusion complexes comprising amino cyclodextrin derivatives in which at least one C2, C3 or C6 hydroxyl is substituted with -NH_2, and a pharmaceutically active agent such as, for example, certain non-steroidal anti-inflammatory drugs, e.g. indomethacin, tolmetin, naproxen,

ketoprofen and the like.

The complex is formed by forming a solution of the cyclodextrin in water or other solvent, which solution is added to a solution of the drug in a solvent, and thereafter removing the solvent. The inclusion complex may be formulated for oral administration.

European Patent Application No. 519 428 to Takeda Chemical Industries teaches a pharmaceutical composition comprising a slightly water-soluble drug, a cyclodextrin and a water-soluble organic solvent in an amount of 0,1 to 10 percent by weight. The composition is prepared in powdered form and is suitable for injection.

South African Patent No. 84/8156 to Chiesi Farmaceutici S.p.A. teaches compounds obtained by complexation of piroxicam with α-β- or α-type cyclodextrins, in ratios comprised between 1:1 and 1:10 of piroxicam and cyclodextrins respectively. The complex may be formulated for oral administration in the form of capsules, tablets, bags, syrups, solutions and the like, including effervescent tablets.

South African Patent No. 91/2282 to Chiesi Farmaceutici S.p.A. teaches a process for preparing piroxicam-cyclodextrin complexes wherein the piroxicam and the cyclodextrin both in powder form are mixed together in a solid state and optionally degassed; the mixture is co-ground in a high energy mill with the grinding chamber saturated with steam; the product obtained is dried under vacuum and screened to eliminate any aggregates. Again the complex produced by this process may be formulated for oral administration for example in the form of tablets which have a much higher

dissolution rate than commercial formulations containing piroxicam alone.

Although many types of inclusion complexes of a cyclodextrin and a non-steroidal anti-inflammatory drug are known, there is always the need for a new type of complex or pharmaceutical composition containing such a complex and a method for the production of such pharmaceutical compositions.

SUMMARY OF THE INVENTION

According to a first aspect of the invention, there is provided a method of making a pharmaceutical composition comprising as an active ingredient an inclusion complex of a β-cyclodextrin or a pharmaceutically acceptable derivative of a β-cyclodextrin and a sparingly water-soluble non-steroidal anti-inflammatory drug, the composition being in solid form which is adapted to be dissolved in water to provide a clear or slightly opaque solution for oral administration, which method includes the steps of:

(a) forming a paste from the β-cyclodextrin or the derivative thereof and the NSAID, with a wetting solution;

(b) mixing the paste with addition of further wetting solution if necessary; and

(c) drying the product of step (b) to produce the inclusion complex which dissolves in water to provide a clear or slightly opaque solution.

According to a second aspect of the invention, there is provided a pharmaceutical composition produced by the method described above.

According to a third aspect of the invention, there is provided a pharmaceutical composition comprising as an active ingredient an inclusion complex of a β-cyclodextrin or a pharmaceutically acceptable derivative of a β-cyclodextrin and a sparingly water-soluble NSAID, the composition being in solid form which is adapted to be dissolved in water to provide a clear or slightly opaque solution for oral administration.

Whenever any reference is made to a drug, there is meant the drug as well as its pharmaceutically acceptable salts.

The pharmaceutical composition in solid form may be in the form of a powder, granule, tablet or sachet.

Examples of suitable β-cyclodextrins or derivatives thereof include β-cyclodextrin, 2-hydroxypropylated-β-cyclodextrin or methylated-β-cyclodextrin. The 2-hydroxypropylated-ß-cyclodextrin preferably has a degree of substitution between 2 and 9, more preferably between 3.9 and 5.1 2-hydroxypropyl groups per ß-cyclodextrin molecule.

Examples of suitable NSAID classes include arylacetic acids, arylpropionic acids, aminoaryl carboxylic acids and thiazine carboxamides. Representative NSAIDs include diclofenac sodium, naproxen, ibuprofen, mefenamic acid, piroxicam, tenoxicam and lornoxicam.

For NSAID's, excluding the thiazine carboxamides, the composition of the

invention is preferably non-effervescent.

Step (a) of the method may comprise mixing the β-cyclodextrin or the derivative thereof in powder form with the NSAID in powder form, and then adding a suitable amount of the wetting solution to the powder mixture to form the paste.

Alternatively, step (a) may comprise mixing the β-cyclodextrin or the derivative thereof in powder form with a suitable amount of the wetting solution to form a paste and then adding the NSAID in powder form or in the form of an aqueous suspension or solution in the wetting solution, with mixing, to the paste.

The molar ratio of NSAID to β-cyclodextrin or the derivative thereof is preferably from 1:1 to 1:5, more preferably from 1:1 to 1:2,5.

The wetting solution may be selected from water, a lower alkanol, preferably ethanol or propanol, or a mixture of water and a lower alkanol. When the wetting solution contains water, it may optionally also contain an amount of an alkali such as sodium hydroxide.

In step (b), the mixing preferably continues for from 0,25 to 5 hours inclusive. During this period, the wetting solution is preferably added periodically to maintain the paste-like consistency of the mixture.

In step (c), the product of step (b) may be dried, for example, under vacuum or in an oven at approximately 40°C.

The method of the invention may include an additional step, after step (c) of:

(d) forming the product of step (c) into a suitable solid pharmaceutical form, optionally with the addition of pharmaceutically acceptable carriers or agents.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 are differential scanning calorimetry (DSC) thermograms of (a) naproxen (b) 2-hydroxypropylated β-cyclodextrin, (c) naproxen/2-hydroxypropylated β-cyclodextrin stoichiometric physical mixture and (d) naproxen/2-hydroxypropylated β-cyclodextrin kneaded complex from Example 2;

Figure 2 are DSC thermograms of (a) ibuprofen (b) methylated β-cyclodextrin, (c) ibuprofen/methylated β-cyclodextrin stoichiometric physical mixture and (d) ibuprofen/methylated β-cyclodextrin kneaded complex from Example 3;

Figure 3 are DSC thermograms of (a) tenoxicam, (b) β-cyclodextrin, (c) tenoxicam/β-cyclodextrin stoichiometric physical mixture, and (d) tenoxicam/β-cyclodextrin kneaded complex from Example 7;

Figure 4 are fourier transform infra-red (FTIR) spectra of (a) diclofenac sodium, (b) β-cyclodextrin, (c) diclofenac sodium/β-cyclodextrin stoichiometric physical mixture, and (d) kneaded inclusion complex from Example 1 - Peak assignments: carboxylate stretch (1); aromatic stretch (2,3);

Figure 5 are FTIR spectra of (a) naproxen, (b) 2-hydroxypropylated β-

cyclodextrin, (c) naproxen/2-hydroxypropylated-β-cyclodextrin stoichiometric physical mixture, and (d) kneaded inclusion complex from Example 2 - Peak assignments: carboxyl stretch (1,2); aromatic stretch (3,4); and
Figure 6 are FTIR spectra of (a) piroxicam, (b) 2-hydroxypropylated β-cyclodextrin, (c) piroxicam/2-hydroxypropylated-β-cyclodextrin stoichiometric physical mixture, and (d) kneaded inclusion complex from Example 6 - Peak Assignments: Amide carbonyl (1); pyridine ring (2); secondary amine (3); aromatic stretch (4).

DESCRIPTION OF EMBODIMENTS

The crux of the invention is a method of making a pharmaceutical composition comprising an inclusion complex of a β-cyclodextrin (BCD) or a pharmaceutically acceptable derivative of a BCD and a sparingly water-soluble NSAID in solid form, which is adapted to be dissolved in water to provide a clear or slightly opaque solution for oral administration which has therapeutic advantages as set out in more detail below.

The method of NSAID-BCD complexation is based on a semi-solid preparation.

In a first stage, the NSAID and cyclodextrin, both in a uniform finely divided powder state, are mixed together in a powder mixer. The particle size of the NSAID and cyclodextrin is preferably less than 250 micron. The molar ratio of NSAID to cyclodextrin is between 1:1 and 1:5, but preferably between 1:1 and 1:2,5.

In a second stage the powder mixture is triturated with appropriate aliquots of a wetting solution to obtain a paste-like consistency. Vigorous mixing is continued for 0,25 to 5 hours maintaining the paste-like consistency by periodic addition of wetting solution. The said wetting solution may be selected from water, a lower alkanol, preferably ethanol or propanol, or a mixture of water and a lower alkanol.

When the wetting solution contains water, it may optionally contain an alkali, preferably sodium hydroxide. The alkali serves two purposes: firstly, it causes ionisation of the NSAID resulting in improved wettability and solubility of the NSAID, and secondly, it enhances the solubility of the cyclodextrin. Together these factors appear to result in more rapid complexation during the kneading process.

On the other hand, ionisation of NSAID's has been shown to reduce the degree of cyclodextrin complexation in solution. However, it has been reported from solution studies that cyclodextrin complexation of ionised NSAID's can result in much larger total NSAID solubilisation, i.e. solubilisation of the NSAID both due to complexation and ionisation, than if either method were used individually (See Reference 12). Thus, the combined use of cyclodextrin complexation together with salt formation of relevant NSAID's provides for a readily soluble form of the NSAID via technically simple methodology.

In an alternative procedure, the NSAID is generally added with mixing to a paste prepared by mixing the cyclodextrin with appropriate aliquots of water which may optionally contain an alkali, preferably sodium hydroxide. The NSAID may be added as a dry powder or suspended or

dissolved in a solution which may contain up to 100 percent v/v of a lower alkanol, preferably ethanol or propanol. Mixing is continued according to the second stage as described above.

In a third stage the product obtained is dried either under vacuum and/or in an oven at 40°C. The dried product is passed through a 30 mesh screen and mixed in a powder mixer.

The final product is characterised by small particle size with significantly enhanced water solubility relative to the pure NSAID. It consists of a NSAID-cyclodextrin molecular inclusion complex. Evidence for the said complex may be demonstrated by differential scanning calorimetric (DSC) and fourier transform infrared (FTIR) spectroscopic analyses.

The solubility characteristics of NSAID-cyclodextrin complexes according to the invention permit the formulation of orally administered pharmaceutical compositions having anti-inflammatory, analgesic and antirheumatic activity. The said formulations have significant advantages over conventional oral NSAID treatments. Because the drug is administered in the dissolved state, the problem of slow NSAID dissolution rate is effectively overcome. Consequently, the time to reach peak plasma concentrations may be significantly reduced resulting in a more rapid onset of therapeutic action. Local gastric irritation due to prolonged contact of the NSAID with the gastrointestinal mucosa is avoided owing to the widespread dispersion of the drug when administered according to the invention. Palatable compositions of the complexes may be simply prepared by mixture of the complex powder with suitable water soluble powder excipients which may include a diluent such as sorbitol or lactose, sweeteners and flavours. The composition may

be in the form of a powder for reconstitution or a soluble tablet, both intended for rapid dissolution in water prior to oral administration. The said compositions are readily soluble in at least 100ml tap water at room temperature. In order that the invention may be more fully understood the following examples relating to the preparation of NSAID-cyclodextrin complexes, their characterisation and pharmaceutical compositions are given.

In the examples which follow, the following compounds are designated as indicated:

Diclofenac sodium	-	(I)
Naproxen	-	(II)
Ibuprofen	-	(III)
Mefenamic acid	-	(IV)
Piroxicam	-	(V)
Tenoxicam	-	(VI)
Lornoxicam	-	(VII)
β-cyclodextrin	-	(BCD)
2-hydroxypropylated β-cyclodextrin	-	(HPB)
Methylated-β-cyclodextrin	-	(MBC)

EXAMPLE 1

BCD and I are passed through 60 mesh screen. BCD (15,6g) is vigorously mixed with deionised water (6ml) to produce a uniform paste. I (4,4g) is slowly added with mixing. Vigorous mixing is continued for 0,25 hour ensuring a uniform paste-like consistency throughout the operation. The mixture is oven dried at 40°C. The dried mass is crushed and passed

through 30 mesh screen. The powder is homogenised in a powder mixer for 10 minutes. The product contains 21,6 percent m/m I with an equilibrium water solubility of 3864mg/100ml as determined by HPLC.

EXAMPLE 2

To 6,0g HPB in a mortar, 4,4ml of a 1N sodium hydroxide solution is added with vigorous mixing to produce a paste. II (1,0g) is passed through a 60 mesh screen and added gradually to the paste with vigorous mixing. The mixture is kneaded for 1 hour with appropriate addition of small aliquots of deionised water to maintain a paste-like consistency. The mixture is oven dried at 40°C. The dried mass is crushed and passed through 30 mesh screen. The powder is homogenised in a powder mixer for 10 minutes. The product contains 13,7 percent m/m II with an equilibrium water solubility of 460mg/100ml as determined by HPLC.

EXAMPLE 3

To 2,5g MBC in a mortar, 3ml propan-1-ol containing 0,4g III is gradually added with vigorous mixing. The mixture is vigorously kneaded for 0,5 hour with appropriate addition of small aliquots of neat propan-1-ol to maintain a paste-like consistency. The mixture is dried under vacuum at 40°C. The dried mass is crushed and passed through a 30 mesh screen. The powder is homogenised in a powder mixer for 10 minutes. The product contains 12,4 percent m/m III with an equilibrium water solubility of 400mg/100ml as determined by HPLC.

EXAMPLE 4

To 6,3g HPB in a mortar, 5ml of a 1N sodium hydroxide solution is added with vigorous mixing to produce a paste. III (1,0g) is passed through a 60 mesh screen and added gradually to the paste with vigorous mixing. The mixture is kneaded for 1 hour with appropriate addition of small aliquots of deionised water to maintain a paste-like consistency. The mixture is dried at 40°C. The dried mass is crushed and passed through a 30 mesh screen. The powder is homogenised in a powder mixer for 10 minutes. The product contains 13,1 percent m/m III with an equilibrium water solubility of 1300mg/100ml as determined by HPLC.

EXAMPLE 5

To 5,7g HPB in a mortar, 4ml of a 1N sodium hydroxide solution is added with vigorous mixing to produce a paste. IV (1,0g) is passed through a 60 mesh screen and added gradually to the paste with vigorous mixing. The mixture is kneaded for 1 hour with appropriate addition of small aliquots of deionised water to maintain a paste-like consistency. The mixture is oven dried at 40°C. The dried mass is crushed and passed through a 30 mesh screen. The powder is homogenised in a powder mixer for 10 minutes. The product contains 14,0 percent m/m IV with an equilibrium water solubility of 430mg/100ml as determined by HPLC.

EXAMPLE 6

HPB (24,0g) and V (2,9g) are passed through 60 mesh screen and tumble mixed for 10 minutes. A 50 percent v/v solution of ethanol in deionised

water (14ml) is gradually added to the mixture with vigorous mixing to produce a uniform paste. Vigorous mixing is continued for 0,3 hours ensuring a uniform paste-like consistency throughout the operation. The mixture is oven dried at 40°C under vacuum. The dried mass is crushed and passed through 30 mesh screen. The powder is homogenised in a powder mixer for 10 minutes. The product contains 9,6 percent m/m V with an equilibrium water solubility of 120mg/100ml as determined by HPLC.

EXAMPLE 7

To 8,7g BCD in a mortar, 7ml deionised water is gradually added with vigorous mixing to produce a paste. VI (1,3g) is passed through a 60 mesh screen and added gradually to the paste with vigorous mixing. The mixture is kneaded for 0,25 hours. The mixture is oven dried at 40°C. The dried mass is crushed and passed through 30 mesh screen. The powder is homogenised in a powder mixer for 10 minutes. The product contains 22,0 percent m/m VI with an equilibrium water solubility of 14mg/100ml as determined by HPLC.

EXAMPLE 8

HPB (2,4g) and VII (0,64g) are passed through 60 mesh screen and tumble mixed for 10 minutes. Deionised water (1-2ml) is gradually added to the mixture with vigorous mixing to produce a uniform paste. Vigorous mixing is continued for 0,3 hours ensuring a uniform paste-like consistency throughout the operation. The mixture is oven dried at 40°C under vacuum. The dried mass is crushed and passed through 30 mesh screen. The powder is homogenised in a powder mixer for 10 minutes. The product contains

20,9 percent m/m VII with an equilibrium water solubility of 14,6mg/100ml as determined by HPLC.

EXAMPLE 9

HPB (21,0g) and IV (2,41g) are passed through a 60 mesh screen and tumble mixed. Deionised water (10ml) is added with vigorous mixing to produce a paste. The mixture is kneaded for 30 minutes with appropriate addition of small aliquots of deionised water to maintain a paste-like consistency. The mixture is vacuum dried at 40°C. The dried mass is crushed and passed through a 30 mesh screen. The powder is homogenised in a powder mixer for 10 minutes. The product contains 10,3 percent m/m IV.

EXAMPLE 10

According to the procedure of Example 1, 2,2g naproxen sodium and 19,8g BCD were used to form a complex containing 10% m/m naproxen sodium.

PHYSICO-CHEMICAL CHARACTERISATION OF NSAID INCLUSION COMPLEXES

Table 1 shows the aqueous solubility of the pure NSAID's (I, III and V) as their stoichiometric cyclodextrin inclusion complexes prepared by kneading and spray drying. It has been shown that inclusion complexes prepared by spray drying represent the best examples in terms of completeness of complexation and highest water solubility (Reference 10). From the table it is evident that the solubility of the complexes prepared according to the

invention compare favourably with the spray dried complexes indicating that acceptable inclusion complexation has taken place.

Table 1 Comparison of the aqueous solubility of NSAID complexes prepared by kneading and spray drying.

Compound	Equilibrium Aqueous Solubility* (mg/100ml) Kneaded Complex**	Spray Dried Complex
I-BCD	3864	4517
III-HPB	1302	3967
V-HPB	120	156

* Determined by HPLC

** Complex from respectively described examples

Differential Scanning Calorimetry (DSC) is the measurement of the rate of heat evolved or absorbed by a sample during a temperature program. The technique may be used to characterise inclusion complexation in cases where the melting point of the included molecule is below the thermal degradation range of the cyclodextrin (i.e. < 250°C). Evidence for inclusion complexation may be obtained from a diminished and/or shifted thermal event corresponding to the melting point of the included guest relative to the pure substance. Compared to the pure NSAID or simple stoichiometric NSAID/cyclodextrin mixtures, representative DSC thermograms of the corresponding kneaded inclusion complexes taken from Examples 2, 3 and 7 show a diminished thermal event corresponding to the melting point of the NSAID as shown in Figures 1 to 3 respectively.

Fourier transform infrared (FTIR) spectroscopy is particularly useful in the characterisation of NSAID/cyclodextrin inclusion complexes owing to the well separated carbonyl band (1680-1730cm^{-1}) or the corresponding ionised carboxylate band (1550-1650cm^{-1}) present in most NSAID's which generally undergoes a frequency shift and/or a reduction in intensity upon inclusion complexation. The former effect is principally due to disruption of intermolecular (NSAID-NSAID) hydrogen bonds whereas the latter effect is due to vibrational restrictions imposed on the guest molecule in the cyclodextrin cavity. Additionally, reduced intensity of bands corresponding to aromatic -C=C- stretching modes (1460-1650 and 680-850cm^{-1}) may also be used as evidence for inclusion complexation. Representative FTIR spectra of kneaded complexes from Examples 1, 2 and 6 show the above phenomena relative to the pure NSAID or the corresponding stoichiometric NSAID/cyclodextrin physical mixture as illustrated in Figures 4 to 6 respectively. In the case of Example 2, it is conceivable that salt formation has taken place with the NSAID carboxyl, in which case the carbonyl group frequency would shift to a shorter wavenumber characteristic of the carboxylate anion. However, the characteristic band of the carbonyl or its corresponding carboxylate are diminished as shown in Figure 5.

PHARMACEUTICAL COMPOSITIONS

EXAMPLE 11

The following formulation was used to prepare readily soluble tablets producing a pleasant tasting clear solution when added to 100ml tap water: Kneaded I-BCD complex from Example 1 was mixed with all other components for 10 minutes, screened through a 30 mesh screen and further

mixed for a suitable time period. The mixture obtained was formed into oval shaped tablets with high surface area. The unit composition of each tablet is as follows:

Kneaded I-BCD complex	120 mg
PEG 6000	5 mg
Spray dried natural orange flavour	30 mg
Sodium cyclamate	30 mg
Sodium saccharin	15 mg
Sorbitol	300 mg
Total :	500 mg

The tablets have a hardness of about 30 N and dissolve with swirling in a time of 3 minutes.

EXAMPLE 12

The following formulation was used to prepare a readily soluble powder producing a pleasant tasting clear solution when added to 100ml tap water: Kneaded II-HPB complex from Example 2 was mixed with all other components for 10 minutes, screened through a 30 mesh screen and further mixed for a suitable time period. The mixture obtained was packed into sachets. The unit composition of each sachet is as follows:

Kneaded II-HPB complex	1465 mg
Sucrose	3365 mg
Spray dried natural cherry flavour	90 mg
Sodium cyclamate	40 mg
Sodium saccharin	40 mg
Total :	5000 mg

EXAMPLE 13

The following formulation was used to prepare a readily soluble powder producing a pleasant tasting slightly opaque solution when added to 100ml tap water: Kneaded III-HPB complex from Example 4 was mixed with all other components for 10 minutes, screened through a 30 mesh screen and further mixed for a suitable time period. The mixture obtained was packed into sachets. The unit composition of each sachet is as follows:

Kneaded III-HPB complex	1524 mg
Spray dried natural cherry flavour	90 mg
Sodium saccharin	115 mg
Total :	1729 mg

EXAMPLE 14

The following formulation was used to prepare a readily soluble powder producing a pleasant tasting slightly opaque solution when added to 100ml tap water: Kneaded V-HPB complex from Example 6 was mixed with all other components for 10 minutes, screened through a 30 mesh screen and

further mixed for a suitable time period. The mixture obtained was packed into sachets. The unit composition of each sachet is as follows:

Kneaded V-HPB complex	210 mg
Spray dried natural orange flavour	5 mg
Sodium saccharin	15 mg
Sodium cyclamate	30 mg
Spray dried lactose	1845 mg
Total :	2000 mg

EXAMPLE 15

The following formulation was used to prepare a readily soluble powder producing a pleasant tasting slightly opaque solution when added to 100ml tap water: Kneaded IV-HPB complex from Example 9 was mixed with the other component for 10 minutes, screened through a 30 mesh screen and further mixed for a suitable time period. The mixture obtained was packed into sachets. The unit composition of each sachet is as follows:

Kneaded IV-HPB complex	2,425 g
Trusil cherry flavour	0.050 g
Total	2,475 g

EXAMPLE 16

The following formulation was used to prepare a readily soluble powder

producing a pleasant tasting slightly opaque solution when added to 100ml tap water: Kneaded naproxen sodium-BCD complex from Example 10 was mixed with the other components for 10 minutes, screened through a 30 mesh screen and further mixed for a suitable time period. The mixture obtained was packed into sachets. The unit composition of each sachet is as follows:

Kneaded naproxen sodium-BCD complex	2,20g
Passion fruit flavour	0,075g
Sodium cyclamate	0.005g
Total	2,280g

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CLAIMS

1 A method of making a pharmaceutical composition comprising as an active ingredient an inclusion complex of a ß-cyclodextrin or a pharmaceutically acceptable derivative of a ß-cyclodextrin and a sparingly water-soluble non-steroidal anti-inflammatory drug, the composition being in solid form which is adapted to be dissolved in water to provide a clear or slightly opaque solution for oral administration, which method includes the steps of:

(a) forming a paste from the ß-cyclodextrin or the derivative thereof and the non-steroidal anti-inflammatory drug, with a wetting solution;

(b) mixing the paste with addition of further wetting solution if necessary; and

(c) drying the product of step (b) to produce the inclusion complex which dissolves in water to provide a clear or slightly opaque solution.

2 A method according to claim 1 wherein the ß-cyclodextrin or the derivative thereof is selected from the group consisting of ß-cyclodextrin, 2-hydroxypropylated-ß-cyclodextrin and methylated-ß-cyclodextrin.

3 A method according to claim 1 or claim 2 wherein the non-steroidal anti-inflammatory drug is selected from the group consisting of an arylacetic acid non-steroidal anti-inflammatory drug, an arylpropionic acid non-steroidal anti-inflammatory drug, an aminoaryl carboxylic

acid non-steroidal anti-inflammatory drug and a thiazine carboxamide non-steroidal anti-inflammatory drug.

4 A method according to claim 3 wherein the non-steroidal anti-inflammatory drug is selected from the group consisting of diclofenac sodium, naproxen, ibuprofen, mefenamic acid, piroxicam, tenoxicam and lornoxicam.

5 A method according to any one of claims 1 to 4 wherein in step (a) the ß-cyclodextrin or the derivative thereof is mixed in powder form with the non-steroidal anti-inflammatory drug in powder form, and there is then added to the powder mixture a suitable amount of the wetting solution to form the paste.

6 A method according to any one of claims 1 to 4 wherein in step (a) the ß-cyclodextrin or the derivative thereof is mixed in powder form with a suitable amount of the wetting solution to form a paste, and there is then added to the paste with mixing the non-steroidal anti-inflammatory drug in powder form or in the form of an aqueous suspension or solution in the wetting solution.

7 A method according to any one of claims 1 to 6 wherein the molar ratio of the non-steroidal anti-inflammatory drug to the ß-cyclodextrin or the derivative thereof is from 1:1 to 1:5.

8 A method according to claim 7 wherein the molar ratio of the non-steroidal anti-inflammatory drug to the ß-cyclodextrin or the derivative thereof is from 1:1 to 1:2,5.

9 A method according to any one of claims 1 to 8 wherein the wetting solution is selected from the group consisting of water, a lower alkanol, and a mixture of water and a lower alkanol.

10 A method according to claim 9 wherein the lower alkanol is selected from the group consisting of ethanol and propanol.

11 A method according to claim 9 or claim 10 wherein when the wetting solution contains water, the wetting solution also contains an amount of an alkali.

12 A method according to claim 11 wherein the alkali is sodium hydroxide.

13 A method according to any one of claims 1 to 12 wherein in step (b) the mixing continues for from 0,25 to 5 hours inclusive.

14 A method according to claim 13 wherein in step (b), the mixing is continued with periodic additions of the wetting solution to maintain the paste-like consistency of the mixture.

15 A method according to any one of claims 1 to 14 wherein step (c) the product of step (b) is dried under vacuum or in an oven at approximately 40°C.

16 A method according to any one of claims 1 to 15 wherein after step (c) there is included step (d) of:

(d) forming the product of step (c) into a suitable solid

pharmaceutical form, optionally with the addition of pharmaceutically acceptable carriers or agents.

17 A pharmaceutical composition comprising as an active ingredient an inclusion complex of a ß-cyclodextrin or a pharmaceutically acceptable derivative of a ß-cyclodextrin and a sparingly water-soluble non-steroidal anti-inflammatory drug, the composition being in solid form which is adapted to be dissolved in water to provide a clear or slightly opaque solution for oral administration.

18 A pharmaceutical composition according to claim 17 wherein the pharmaceutical composition is made by a method which includes the steps of:

(a) forming a paste from the ß-cyclodextrin or the derivative thereof and the non-steroidal anti-inflammatory drug, with a wetting solution;

(b) mixing the paste with addition of further wetting solution if necessary; and

(c) drying the product of step (b) to produce the inclusion complex which dissolves in water to produce a clear or slightly opaque solution.

19 A pharmaceutical composition according to claim 17 or claim 18 wherein the ß-cyclodextrin or the derivative thereof is selected from the group consisting of ß-cyclodextrin, 2-hydroxypropylated-ß-cyclodextrin and methylated-ß-cyclodextrin.

20 A pharmaceutical composition according to any one of claims 17 to

19 wherein the non-steroidal anti-inflammatory drug is selected from the group consisting of an arylacetic acid non-steroidal anti-inflammatory drug, an arylpropionic acid non-steroidal anti-inflammatory drug, an aminoaryl carboxylic acid non-steroidal anti-inflammatory drug, and a thiazine carboxamide non-steroidal anti-inflammatory drug.

21 A pharmaceutical composition according to claim 20 wherein the non-steroidal anti-inflammatory drug is selected from the group consisting of diclofenac sodium, naproxen, ibuprofen, mefenamic acid, piroxicam, tenoxicam and lornoxicam.

22 A pharmaceutical composition according to any one of claims 18 to 21 wherein in step (a) the ß-cyclodextrin or the derivative thereof is mixed in powder form with the non-steroidal anti-inflammatory drug in powder form, and there is then added to the powder mixture a suitable amount of the wetting solution to form the paste.

23 A pharmaceutical composition according to any one of claims 18 to 21 wherein in step (a) the ß-cyclodextrin or the derivative thereof is mixed in powder form with a suitable amount of the wetting solution to form a paste, and there is then added to the paste with mixing the non-steroidal anti-inflammatory drug in powder form or in the form of an aqueous suspension or solution in the wetting solution.

24 A pharmaceutical composition according to any one of claims 17 to 23 wherein the molar ratio of the non-steroidal anti-inflammatory drug to the ß-cyclodextrin or the derivative thereof is from 1:1 to

1:5.

25 A pharmaceutical composition according to claim 24 wherein the molar ratio of the non-steroidal anti-inflammatory drug to the ß-cyclodextrin or the derivative thereof is from 1:1 to 1:2,5.

26 A pharmaceutical composition according to any one of claims 18 to 25 wherein the wetting solution is selected from the group consisting of water, a lower alkanol, and a mixture of water and a lower alkanol.

27 A pharmaceutical composition according to claim 26 wherein the lower alkanol is selected from the group consisting of ethanol and propanol.

28 A pharmaceutical composition according to claim 26 or claim 27 wherein when the wetting solution contains water, the wetting solution also contains an amount of an alkali.

29 A pharmaceutical composition according to claim 28 wherein the alkali is sodium hydroxide.

30 A pharmaceutical composition according to any one of claims 18 to 29 wherein in step (b) the mixing continues for from 0,25 to 5 hours inclusive.

31 A pharmaceutical composition according to claim 30 wherein in step (b), the mixing is continued with periodic additions of the wetting

solution to maintain the paste-like consistency of the mixture.

32 A pharmaceutical composition according to any one of claims 18 to 31 wherein in step (c) the product of step (b) is dried under vacuum or in an oven at approximately 40°C.

33 A pharmaceutical composition according to any one of claims 18 to 32 wherein the method includes after step (c), step (d) of:

(d) forming the product of step (c) into a suitable solid pharmaceutical form, optionally with the addition of pharmaceutically acceptable carriers or agents.

34 A pharmaceutical composition according to any one of claims 17 to 33 in the form of a powder, granule, tablet or sachet.

Fig 1

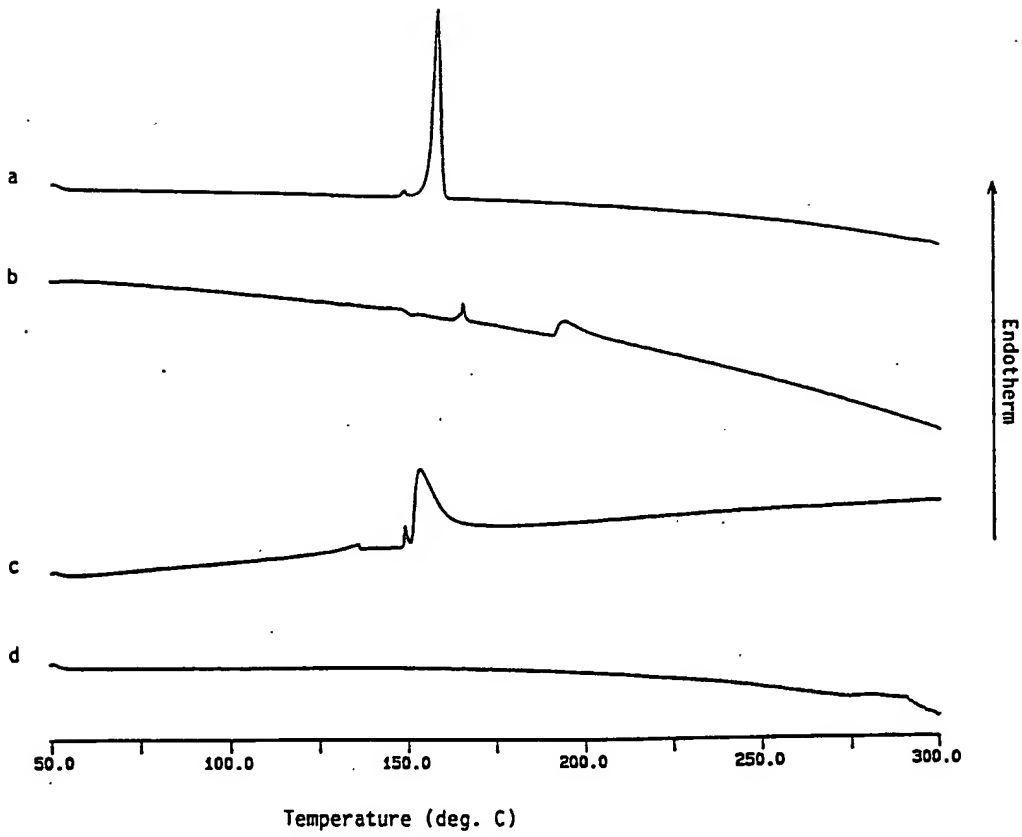
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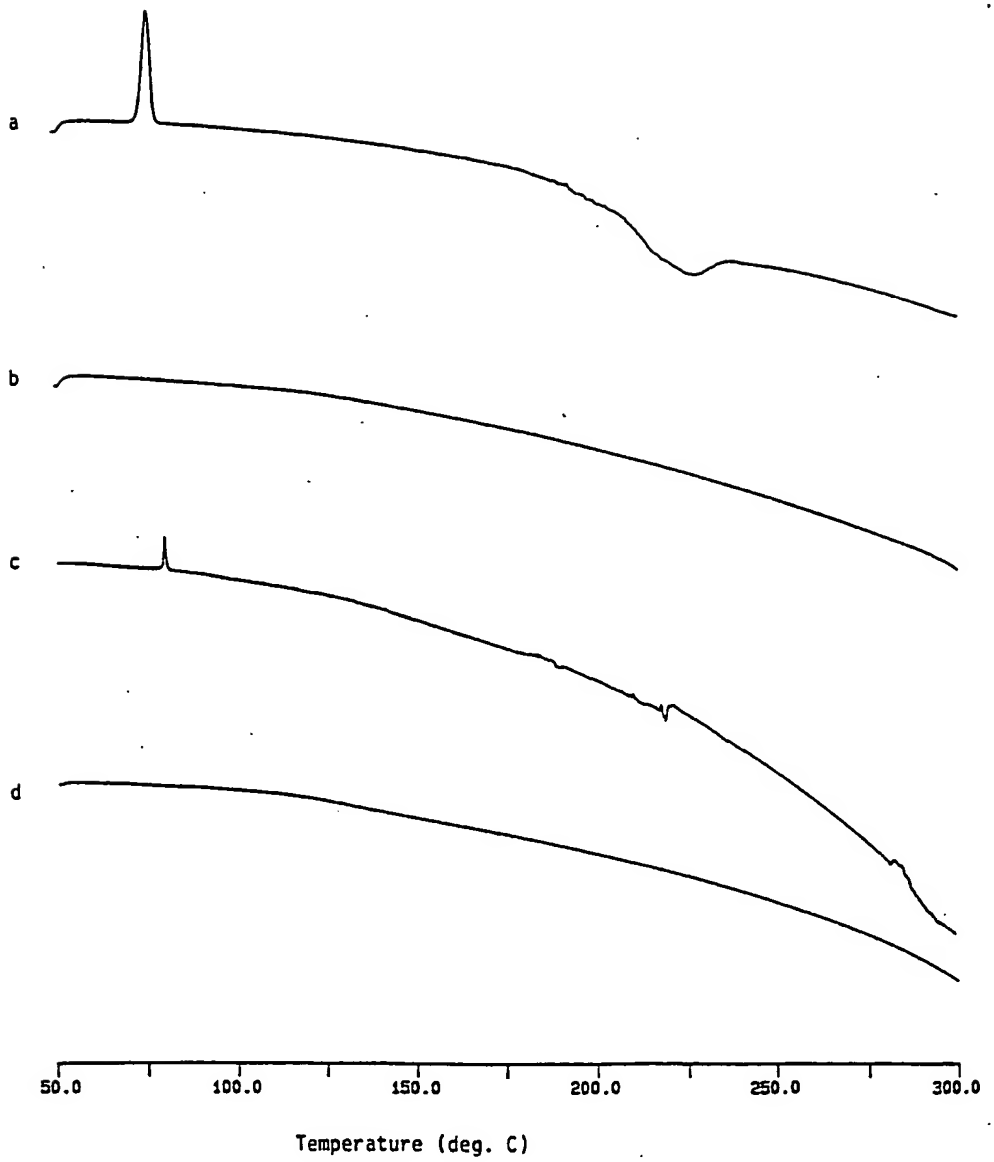
Fig 2



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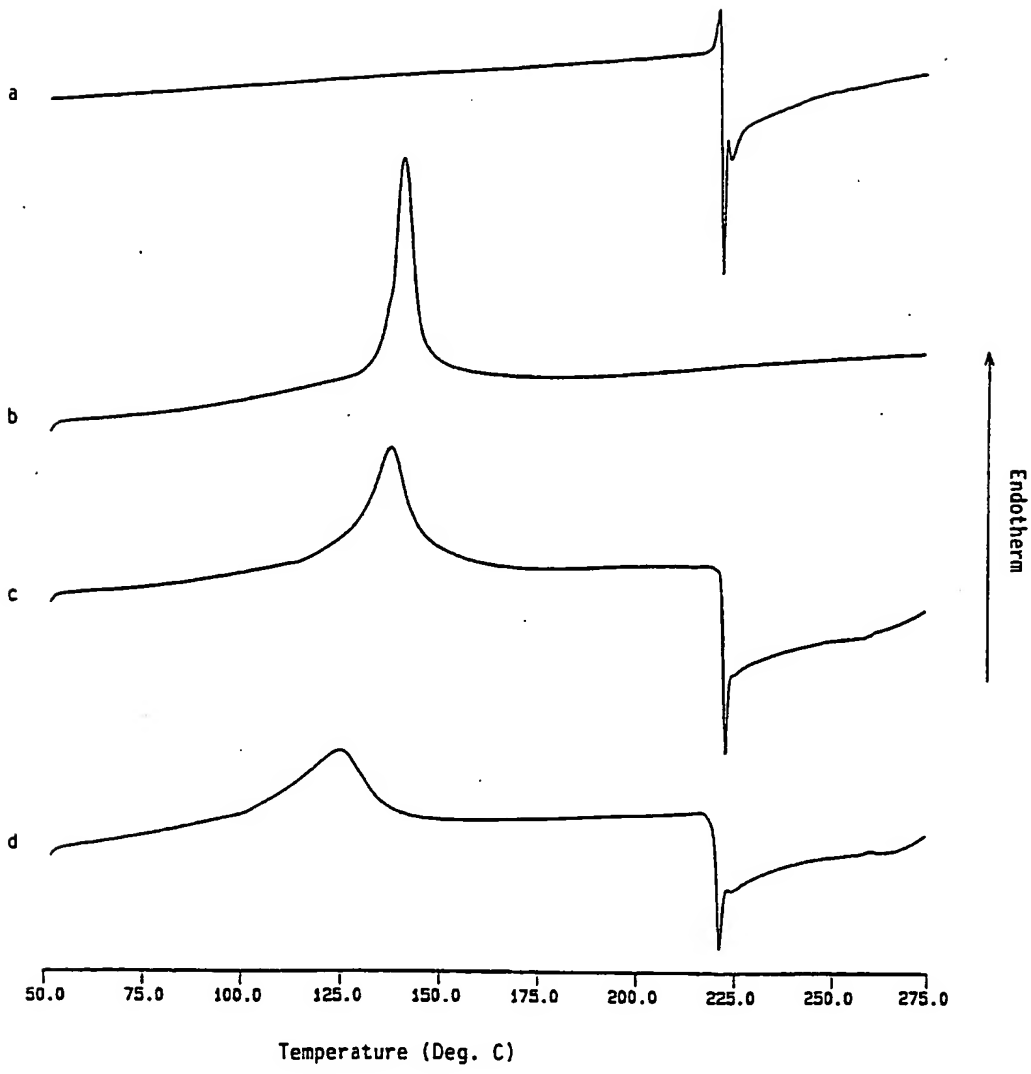
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Temperature (Deg. C)

Fig 4

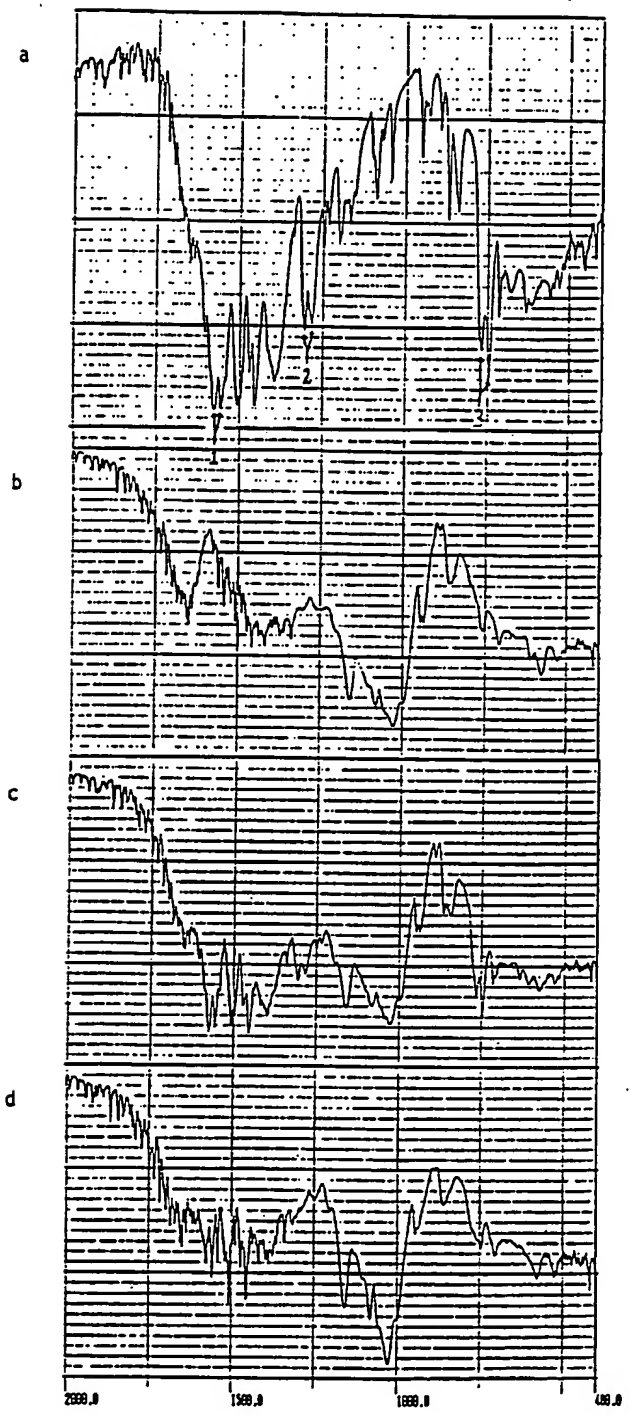


Fig 5

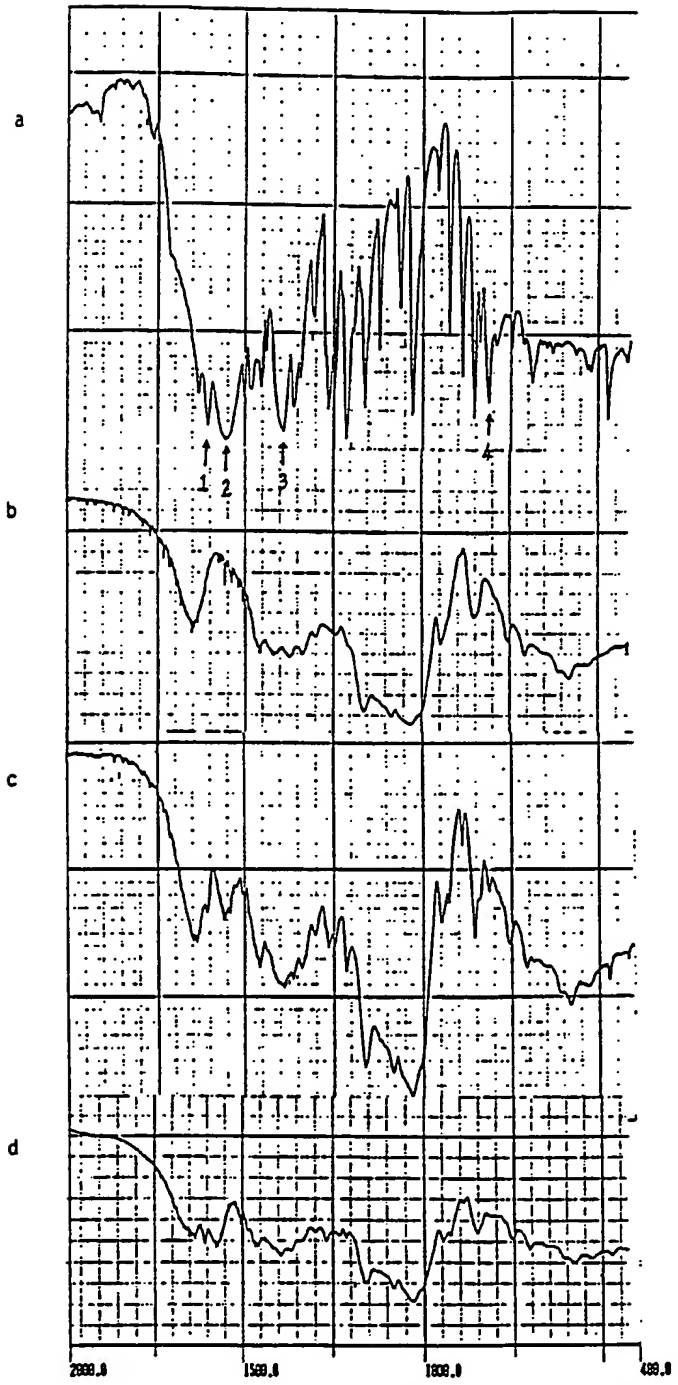
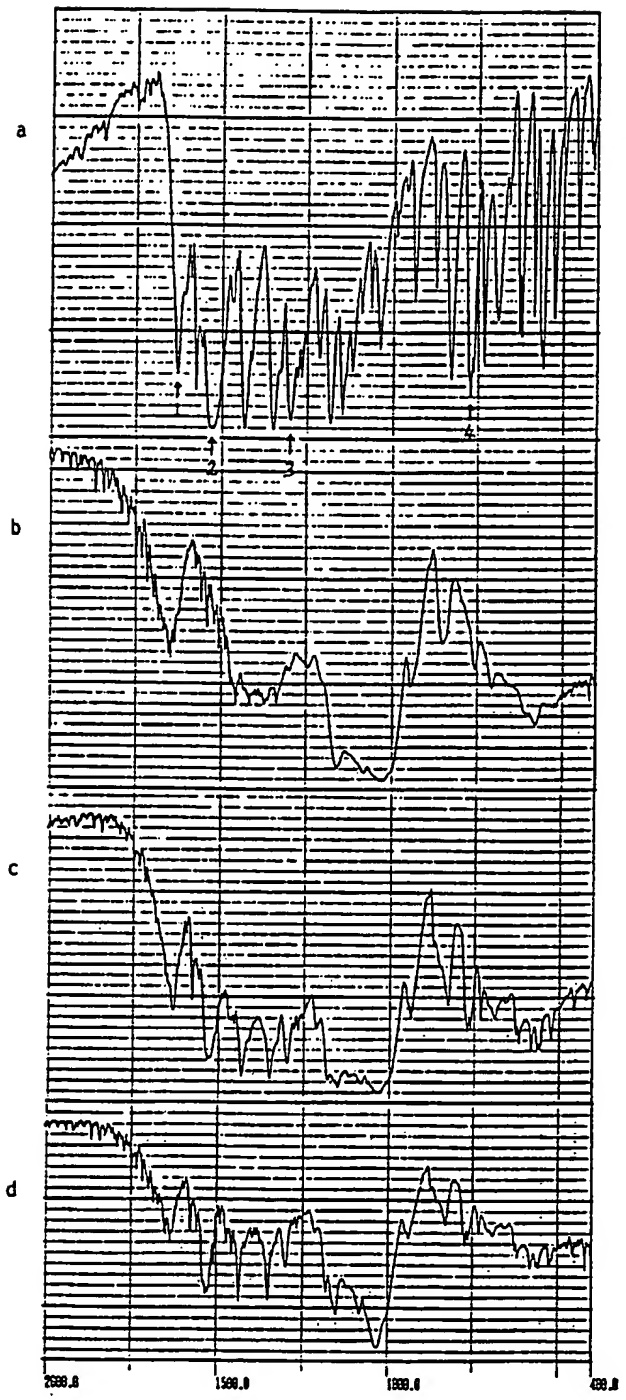


Fig 6



INTERNATIONAL SEARCH REPORT

Internatic Application No PCT/GB 95/01152

A. CLASSIFICATION OF SUBJECT MATTER
A 61 K 47/40

According to International Patent Classification (IPC) or to both national classification and IPC 6

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A 61 K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
30 June 1995	04.08.1995

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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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ANHANG — ANNEX — ANNEXE

zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

to the International Search Report to the International Patent Application No.

au rapport de recherche international relatif à la demande de brevet international n°

PCT/GB 95/01152 SAE 110063

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

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				EP	A2	149197	24-07-85
				EP	A3	149197	14-08-85
				EP	B1	149197	21-03-90
				FI	A	853198	20-08-85
				FI	A0	853198	20-08-85
				FI	B	86140	15-04-92
				FI	C	86140	27-07-92
				HK	A	1312/93	03-12-93
				HU	A2	40561	28-01-87
				HU	B	200943	28-09-90
				JP	T2	61500788	24-04-86
				JP	B4	5070612	05-10-93
				KR	B1	9208700	08-10-92
				NO	A	853070	02-08-85
				NO	B	171888	08-02-93
				NO	C	171888	19-05-93
				SG	A	248/93	06-08-93

			ZA	A	8410042	25-09-85
EP A1	153998		AT	E	52263	15-05-90
			AU	A1	38923785	29-08-85
			AU	B2	550007	27-02-86
			BE	A1	900836	15-02-85
			CA	A1	1234106	15-03-88
			DE	C0	3482041	31-05-90
			DK	A0	760/85	19-02-85
			DK	A	760/85	23-08-85
			DK	B	164911	07-09-92
			DK	C	164911	18-01-93
			EP	A2	153998	11-09-85
			EP	TD	153998	10-04-86
			EP	A3	153998	14-01-87
			EP	B1	153998	25-04-90
			ES	A1	536909	01-05-85
			ES	A5	536909	28-05-85
			ES	A1	8504789	16-07-85
			IE	B	58231	11-08-93
			IT	A0	8419735	22-02-84
			IT	A	1196033	10-11-88
			JP	A2	60208979	21-10-85
			JP	B4	3070705	08-11-91
			KR	B1	8701960	23-10-87
			NZ	A	211114	30-09-87
			PH	A	22075	20-05-88
			PT	A	79997	01-03-85
			PT	B	79997	13-01-87
			SG	A	536/90	23-11-90
			US	A	4603123	29-07-86
			ZA	A	8408156	26-06-85
EP A2	519428	23-12-92	CA	AA	2071623	22-12-92
			EP	A3	519428	24-02-93
			EP	A3	519428	05-05-93
			JP	A2	5178765	20-07-93